Article published online: 2023-05-08

Hepatic Innervations and Nonalcoholic Fatty Liver Disease

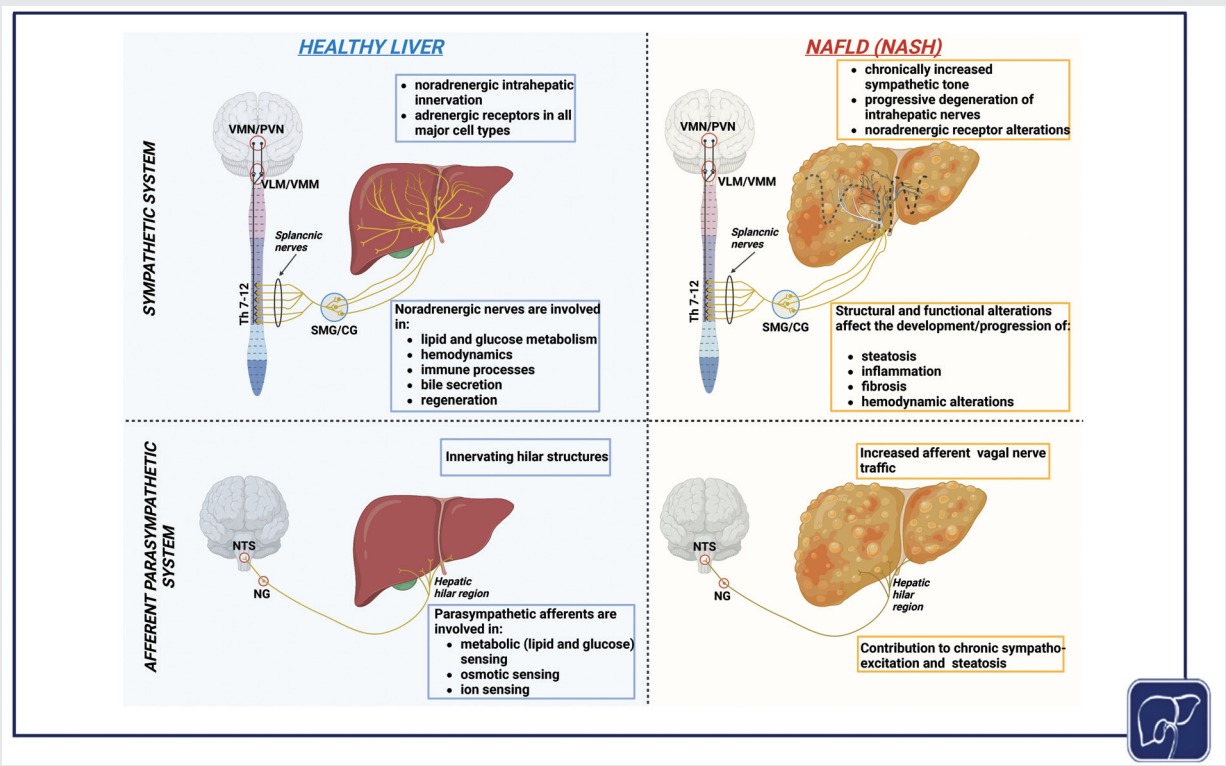
Monika Adori, PhD[1] Sadam Bhat, MSc[2] Roberto Gramignoli, PhD[3] Ismael Valladolid-Acebes, PhD[4] Tore Bengtsson, PhD[5] Mathias Uhlèn, PhD[6,7] Csaba Adori, PhD[5,6]

[1] Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden
[2] Department of Molecular and Cellular Medicine, Institute of Liver and Biliary Sciences, New Delhi, India
[3] Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden
[4] Department of Molecular Medicine and Surgery, The Rolf Luft Research Center for Diabetes and Endocrinology, Karolinska Institutet, Stockholm, Sweden
[5] Department of Molecular Biosciences, The Wenner-Gren Institute (MBW), Stockholm University, Stockholm, Sweden
[6] Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden
[7] Science for Life Laboratory, Royal Institute of Technology, Stockholm, Sweden

Address for correspondence Csaba Adori, PhD, Department of Molecular Biosciences - The Wenner-Gren Institute (MBW), Svante Arrhenius väg 20C, 114 18, Stockholm, Sweden; Department of Neuroscience, Karolinska Institutet, Solnavägen 9, 171 65 Solna, Sweden (e-mail: adorics@gmail.com; csaba.adori@ki.se).

Semin Liver Dis 2023;43:149–162.

Graphical Abstract



Abbreviations: VMN/PVN, hypothalamic ventromedial nucleus/paraventricular nucleus; VLM/VMM, ventrolateral medulla/ventromedial medulla; SMG/CG, superior mesenteric ganglion/caeliac ganglia; NTS, nucleus of the solitary tract; NG, nodose ganglion.

article published online
May 8, 2023

DOI https://doi.org/10.1055/s-0043-57237.
ISSN 0272-8087.

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disorder. Increased sympathetic (noradrenergic) nerve tone has a complex role in the etiopathomechanism of NAFLD, affecting the development/progression of steatosis, inflammation, fibrosis, and liver hemodynamical alterations. Also, lipid sensing by vagal afferent fibers is an important player in the development of hepatic steatosis. Moreover, disorganization and progressive degeneration of liver sympathetic nerves were recently described in human and experimental NAFLD. These structural alterations likely come along with impaired liver sympathetic nerve functionality and lack of adequate hepatic noradrenergic signaling. Here, we first overview the anatomy and physiology of liver nerves. Then, we discuss the nerve impairments in NAFLD and their pathophysiological consequences in hepatic metabolism, inflammation, fibrosis, and hemodynamics. We conclude that further studies considering the spatial-temporal dynamics of structural and functional changes in the hepatic nervous system may lead to more targeted pharmacotherapeutic advances in NAFLD.

Keywords

- nonalcoholic fatty liver disease
- sympathetic nerves
- parasympathetic nerves
- noradrenaline
- steatosis
- inflammation
- fibrosis
- portal hypertension

Lay Summary

Nonalcoholic fatty liver disease (NAFLD) is the most common hepatic disorder, with prevalence around 25% globally. Nearly 70% of patients with type-2 diabetes have fatty liver, and NAFLD is associated with heart and kidney complications. Currently, the therapeutic options are limited to lifestyle changes and no universally approved drug therapy exists for NAFLD. Nerve fibers in the liver play a complex role in liver fat and sugar metabolism, blood circulation, immune responses, and bile secretion. Previous research revealed structural and functional impairments of the liver nerves in NAFLD, which contribute to fat accumulation, inflammation, and abnormal growth of fibrous connective tissue in the diseased liver. Here, we overview the anatomy and physiology of liver nerves and discuss the nerve alterations, with their potential causes and consequences in NAFLD. We emphasize that deeper understanding of structural and functional changes in the liver nervous system in NAFLD may lead to new targeted therapeutic interventions.

Nonalcoholic Fatty Liver Disease: Symptoms, Pathogenesis, and the Role of Hepatic Innervations

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disorder, with a prevalence of approximately 25 to 30% in the Western countries.[1–3] NAFLD is a systemic disease and it is considered as the hepatic manifestation of the metabolic syndrome. NAFLD is usually associated with visceral obesity, insulin resistance, increased blood pressure, fasting hyperglycemia, and dyslipidemia.[3] Nearly 70% of type-2 diabetes patients have NAFLD comorbidity.[4] Moreover, NAFLD is associated with renal and cardiovascular complications.[5] Indeed, the most common cause of death in NAFLD is cardiovascular-related.[6] Currently, the therapeutic options are palliative, limited to lifestyle and dietary changes, with no consensus on pharmacological therapy.

The spectrum of NAFLD may vary from early-onset steatosis (intrahepatic triglyceride accumulation), via nonalcoholic steatohepatitis (NASH; up to 30% of all NAFLD cases),[7,8] to end-stage liver cirrhosis and hepatocellular carcinoma.[9] Mild forms of liver steatosis can be considered as a relatively benign condition; however, NASH is a severe disease, which is characterized by large-scale steatosis, chronic lobular inflammation, hepatocellular injury, and progressive fibrosis.[9]

The pathogenesis of NAFLD implies initial metabolic disturbances, such as insulin resistance, which may lead to steatosis. The transition between steatosis and NASH could be described by a "multiple-hit" model. Namely, impaired lipid partitioning, oxidative stress caused by lipotoxicity, proinflammatory cytokine-mediated hepatocyte injury and cell death, as well as further metabolic abnormalities may contribute to the development of NASH.[10] Since NAFLD is the hepatic manifestation of a multisystem metabolic disorder that is heterogeneous in its underlying causes and presentation, some authors recently suggested calling it as "metabolic dysfunction-associated fatty liver disease" (MAFLD).[11]

The liver has a complex innervation with significant interspecies differences among mammalian species. Anatomical and physiological studies revealed that efferent hepatic innervations have a complex role in the regulation of liver lipid and glucose metabolism, hemodynamics, immune-processes, bile secretion, and tissue regeneration. Furthermore, sensory (afferent) liver nerves play important role in metabolic (glucose and lipid) sensing, osmotic sensing, and ion sensing.[12–15]

Despite such relevance, hepatic innervations have been understudied until recently, especially concerning their potential involvement in liver pathologies. This was perhaps because of methodical limitations in manipulating and visualizing hepatic nerves, or because liver functions did not appear seriously compromised after orthotopic liver transplantation (OLT).[16] However, long-term follow-up studies

described dyslipidemia, postprandial hyperglycemia, insulin resistance, and alterations in intrahepatic microcirculation after OLT.[12,17,18] Furthermore, postprandial hyperglycemia was exaggerated and lasted longer in liver transplant patients than in kidney-transplanted individuals who also underwent immunosuppressive medications.[19] This raises the possibility that the inevitable liver denervation in OLT may contribute to the development of the post-transplantation metabolic syndrome. Nonetheless, further studies are needed to examine this question in more detail.

Recent functional and structural investigations using selective stimulation of hepatic sympathetic nerves,[20] pharmacological methods targeting liver adrenergic receptors,[21] as well as high-resolution and large-scale 3D visualization of hepatic nerves by state-of-the-art volume imaging[22,23] have highlighted a significant role of liver nerves in NAFLD pathophysiology. This review first overviews the anatomy and physiology of liver nerves and the intrahepatic nerve-mediated cellular communication. Then, liver nerve structural and functional alterations in NAFLD will be discussed, and finally potential causes and consequences of all these nerve-related pathologies will be elucidated.

Hepatic Nerves and the Intrahepatic Nerve-Mediated Cellular Communication

The Roman physician and philosopher Galen already mentioned liver nerves in one of his works.[24] The first more detailed descriptions of mammalian hepatic innervations go back to the mid-19th century.[25]

The liver does not contain neural crest-derived intrinsic neurons[26] but receives sympathetic efferent innervations from the splanchnic nerves, parasympathetic efferent and afferent innervations from the vagus nerve, and spinal afferent innervations from the dorsal root ganglia.

During fetal life, the primary role of the liver is hematopoietic, and only sparse hepatic innervations are noticed, especially in rodents.[26] NPY-positive (sympathetic) fibers were first found at embryonic day 19 (E19) in the mouse liver.[27] In another study, no intrahepatic nerves were described in the mouse at E17.5 and at postnatal day 1 (P1) by using tubulin β 3 class III (TUBB3), a pan-neuronal marker. Nerves were first noticed at P7 in the liver surrounding the intrahepatic bile ducts, and they gradually populated the liver by P21. The intrahepatic bile ducts guided the extension of nerve fibers by secreting nerve growth factor during development.[28] According to a recent report in mice, using another pan-neuronal marker, protein gene product 9.5 (PGP9.5), nerves first appeared at the hilum at E16.5 and gradually populated the entire lobes toward their periphery by P28. The authors concluded that the interaction between nerves, intrahepatic bile ducts, and hepatic artery plays an important role in the morphogenesis and stabilization of portal structures.[29] In humans, the first hepatic nerves were noticed on the 8 to 12th gestation weeks, around the portal tracts, as identified by PGP9.5, neuron-specific enolase, and neurofilament pan-neuronal markers. These nerves gradually increased in density and reached the adult level by the 32 to 33rd gestation weeks. However, intraparenchymal thin fibers appeared only at term (40th week).[30]

Centrally, the descending liver sympathetic projections arise from pre-autonomic neurons of the ventromedial hypothalamic nucleus and paraventricular nucleus (PVN),[31,32] projecting to the ventrolateral and ventromedial medullary reticular formation. Neurons of this medullary autonomic center project to cholinergic preganglionic neurons in the intermediolateral column of the thoracic spinal cord (Th7–Th12). Preganglionic splanchnic nerve fibers then innervate the noradrenergic superior mesenteric ganglion and celiac ganglia, which send postganglionic innervations toward the liver. The nerves enter the liver in the hilum and then follow the portal triads. The major nerve fibers localize around larger intrahepatic bile ducts and the hepatic artery. Such primary fibers give rise to a thin, spiderweb-like nerve plexus, which wraps around all the bile ducts as well as branches of the hepatic artery and portal vein (►**Fig. 1A**). Spatially, this noradrenergic nerve plexus terminates approximately 100 to 200 µm ahead of the most distal parts of the portal veins, 300 to 400 µm below the organ surface.[22] Fine nerve filaments follow extracellular matrix (ECM) collagen fibers within the Glisson's sheath, in close contact with vascular smooth muscle cells, endothelial cells, and biliary epithelial cells.[22] No significant innervation has been detected around the central veins or the hepatic vein.[33] However, bolstered by advanced 3D imaging technology, we have been able to elucidate a limited innervation of central veins in mouse. Such nerve fibers originate from the adjacent periportal nerve plexus: bridging fibers branch again and extend for a few hundred micrometers around the central veins.[22] The periportal innervation is described in all examined mammalian species; however, there are significant interspecies differences reported regarding the parenchymal innervation. Namely, while the sympathetic innervation in healthy conditions is restricted to the periportal region in mouse and rat, fine noradrenergic fibers enter the liver parenchyma in human, monkey, cat, dog, guinea pig, and rabbit.[34–36] In our recent work, we have explored the parenchymal innervation in more detail in humans. 3D imaging showed that the periportal nerves give rise to "interlobular" nerve fibers running in the interlobular connective tissue septae (►**Fig. 1B**). Such nerves give rise to 3- to 6-µm-thin fine varicose fibers that run in the perisinusoidal (Disse) space, following ECM collagen III^{+} fibers, with decreasing density toward the centrolobular zone 3.[22] Previous electron microscopy (ELMI) studies revealed that these nerve filaments are nonmyelinated and frequently glial sheath-free. They form neuroeffector junctions, without synaptic specializations, with both parenchymal cells (hepatocytes) and nonparenchymal cells (endothelial-, Kupffer-, and hepatic stellate- [Ito] cells).[27,37,38] The hepatic noradrenergic fibers co-localize with the neuropeptides NPY and galanin.[22,39]

Centrally, the liver efferent parasympathetic projections arise from neurons in the lateral hypothalamic area, which project to the dorsal motor nucleus of the vagus and the ambiguous complex.[31,32,40] These nuclei supply the preganglionic vagal efferents. Afferent (sensory) vagal nerves are

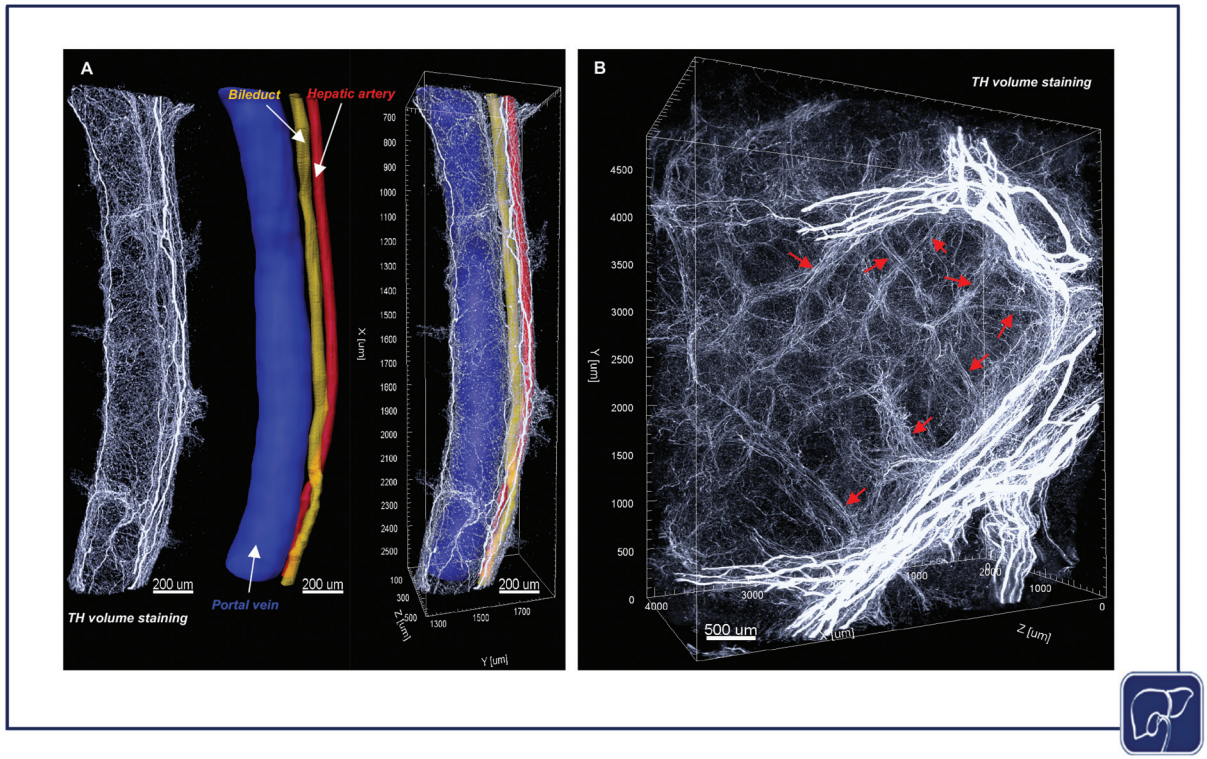


Fig. 1 Sympathetic innervation of the mouse and human liver. (**A**) Periportal sympathetic nerves in the mouse liver are visualized by tyrosine hydroxylase (TH) volume immunostaining. *Left panel*: TH staining; *middle panel*: elements of the portal triad are segmented and color-coded based on autofluorescence; *right panel*: sympathetic nerves around the segmented elements of the portal triad. (**B**) TH volume immunostaining of a $5 \times 5 \times 2$ mm piece of healthy human liver. Note the extensive thick nerve fibers around the portal triad and the interlobular branches (*arrows*) that arise from the periportal nerve plexus. From these interlobular nerves, fine intraparenchymal fibers target the parenchyma. (Micrographs are from Adori et al.[22])

supposed to be derived from the nodose ganglion.[41] Nodose ganglion neurons then project to the medullary nucleus of the solitary tract. The common hepatic branch of the vagus bifurcates to the larger gastroduodenal branch, targeting the pancreas and gut, while the minor hepatic branch proper targets the liver hilum. So far, however, no clear documentation of intrahepatic parasympathetic ganglia has been provided. Moreover, we and others were unable to detect intrinsic parasympathetic (cholinergic) innervation, both in rodents[22,23] and in primates or humans.[23] Earlier studies described intrahepatic cholinergic nerves based on acetylcholinesterase histochemistry.[36,42] However, this method cannot be considered fully specific and reliable for visualizing cholinergic fibers.[38] More specific vesicular acetylcholine transporter immunohistochemistry or green fluorescent protein (GFP) immunostaining of choline-acetyltransferase (ChAT)-GFP mice failed to show any intrinsic hepatic cholinergic nerves.[22,43] Based on tracing techniques, a few vagal efferent fibers were found within the fascicles of the vagal hepatic branch and in a small fraction of vagal paraganglia in the rat. Regarding vagal afferents, fibers were noticed around larger portal triads in the hilum of different liver lobes, around the extrahepatic part of the portal vein, and around almost all paraganglia adjacent to the hepatic branch of the vagus and the hilum.[41,44] Overall, (mainly afferent) parasympathetic hepatic innervations may be restricted to hilar structures, while a direct hepatic cholinergic innervation is doubtful. Some authors propose an indirect vagal control of the liver, by affecting the sympathetic celiac ganglion or microganglia around the celiac artery. Such hypothesis is supported by the demonstration of vagal preganglionic terminals in these structures.[45] However, further detailed and comparative studies are needed to elicit the anatomy of the liver parasympathetic innervations.

Spinal afferent innervation of the liver is provided by lower thoracic (Th7–Th12) dorsal root ganglia (DRG) neurons. The neuropeptides calcitonin gene-related peptide (CGRP) and substance P are markers to visualize these fibers.[46] CGRP volume immunostaining identified sparse innervations around portal triads, but no $CGRP^+$ nerves were found in the parenchyma or around the central veins in mice.[22]

Between hepatocytes, nerve signals can be propagated via gap junctions. Electric coupling of hepatocytes by gap junctions is relevant also in the human liver, but it is particularly important in rodents where the nerves are restricted to the periportal area.[47] In mice and rats, the nerves are in contact only with a few periportal hepatocytes, and then the nerve-derived signal is propagated via gap junctions. The major gap junction protein in the liver is connexin 32 (CX32).[48] Gap junction inhibitors in rats completely blocked the nerve-mediated metabolic- and hemodynamic alterations.[47] Moreover, in CX32-deficient mice, dilated bile canaliculi have been observed and a

decrease in bile flow was described after electric stimulation of sympathetic nerves.[49]

G-coupled noradrenergic receptors are expressed by virtually all major cell types in the mammalian liver. Namely, α and β receptor expressions were described in hepatocytes.[50–52] In primary cultures, hepatic stellate cells (HSCs) express α1a, α1b, α1d, α2b, β1, β2, β3, and NPY receptors.[53–55] The liver resident macrophage Kupffer cells were reported to express all the nine adrenergic reports.[56] Liver progenitor cells express α1 receptors.[57] Moreover, α and β receptors in the portal vein wall, as well as α receptors in all segments of the liver vasculature, were described.[58,59] In a more detailed study, β3 receptors were shown in the portal vein endothelium and muscle cells in mice.[60] Cholangiocytes express α1 forms (a, b, and d)[61] and β2[62] receptors. More detailed information concerning adrenergic receptor expressions in various hepatic cell types is reported in a single cell RNA sequencing study of the human liver[63] and in a recent detailed review.[64] In addition to the noradrenergic receptors, nicotinic[65] and muscarinic (M1–M5)[66] cholinergic receptors were also described in HSCs. Sensory receptive mechanisms on the molecular level are much less explored in the liver. In case of osmotic sensing, Lechner et al identified transient receptor potential channel member 1 ion channels in DRG-derived spinal sensory nerve fibers in the mouse liver, which detect physiological changes in blood osmolality.[67]

Vegetative Imbalance and Its Role in NAFLD Pathogenesis

Besides sedentary lifestyle, unhealthy diet, or genetic predisposing factors, several studies highlight an autonomic imbalance, namely, an increased sympathetic nerve tone, as a key factor in the etiopathogenesis of NAFLD.[68–70] Such increased sympathetic tone may be the consequence of enhanced excitability and overactivity of liver-related preautonomic neurons in the hypothalamic PVN.[71] In guanine nucleotide exchange factor 3 (Vav3) knockout mice with chronic sympathetic hyperexcitation, the metabolic syndrome and fatty liver onset were noted already at 4 months of age, progressing to NASH without obesity after 1 year in animals kept on normal chow diet.[72] A recent study depicted a more direct pathogenic link between liver sympathetic outflow and hepatic steatosis, the initial manifestation of NAFLD.[20] Namely, high fat diet–induced NAFLD in mice was associated with doubling of firing rate in efferent liver sympathetic nerves. Furthermore, the steatosis was effectively reversed with chemical sympathectomy, independently of overall weight changes, caloric intake, or adiposity.

Chronically high sympathetic tone in NAFLD was confirmed also in humans. One study on 2,000 participants concluded that increased sympathetic and decreased parasympathetic activities, rather than changes in hypothalamic–pituitary–adrenal (HPA) axis, are associated with the metabolic syndrome.[69] A recent large-scale study with 34,000 participants showed decreased parasympathetic activity and elevated sympathetic tone as an increased risk for NAFLD.[73] Another study in a smaller cohort of participants demonstrated that NAFLD was associated with cardiac sympathetic/parasympathetic imbalance assessed by heart rate variability, regardless of the presence or absence of type-2 diabetes.[74]

Finally, chronically elevated sympathetic tone in the liver has systemic consequences as well. It leads to increased hepatic arteriolar resistance, affecting renal sympathetic activation, with consequence of renal arteriolar vasoconstriction and renin–angiotensin–aldosterone system (RAAS) activation. This hepatorenal reflex that mediates RAAS activation further decreases the renal blood flow and glomerular filtration, and increases systemic sodium retention[75] with possible further cardiovascular consequences.

Liver Nerve Pathologies and Receptor Alterations in NAFLD

The NAFLD spectrum is associated with pathologies of the hepatic nerves. Early studies showed decreased densities of liver innervations in cirrhosis, mainly in the parenchyma.[76–81] Moreover, liver sympathetic nerve density decreased in male macaques exposed to perinatal high fat diet (combination of high fat diet to mothers and early postnatal high fat diet to offspring).[82]

More detailed examination of hepatic nerve pathologies was possible with the recent application of volume immunostaining and light sheet microscopy. Using such novel 3D imaging technique, we showed parallel signs of mild axonal trimming and sprouting of sympathetic nerve fibers in steatosis, which turns to a severe degeneration of nerves in steatohepatitis in mice (►**Fig. 2A–D**).[22] Aberrantly spouting fibers in steatosis showed ectopic parenchymal localization and they followed collagen fibers. In parallel, hepatic NFG expression was elevated, suggesting that hepatic sympathetic nerves exhibit an increased plasticity in the early steatosis onset. This may be the consequence of a starting reorganization of the ECM, which, in turn, destabilizes the mechanical support of collagen fibers to the nerve filaments.[22] Notably, ECM reorganization is an early, critical event in fibrosis, and it starts much earlier than the cirrhotic stage in the NAFLD spectrum.[83] Degenerating sympathetic nerve fibers, which appeared in significant amounts typically in the more advanced steatohepatitis, showed swollen axonal pathology indicating an axo-plasmatic transport problem. Namely, fine unmyelinated varicose fibers are particularly sensitive for oxidative stress that may be a consequence of chronic nerve activity, lipotoxicity, and proinflammatory immune processes. Oxidative stress leads to the destruction of microtubules, causing axo-plasmatic transport impairments in the nerves.[84–86] Human fatty livers showed similar nerve damages that was observed in mice, starting with the finest intraparenchymal fibers, and correlating with the severity of NAFLD pathology (►**Fig. 2E**). Chronically high sympathetic tone is a key factor in this degeneration—as we showed similar fiber degeneration in the VaV3 knockout mouse line with chronic sympathoexcitation.[22] Liver sympathetic neuropathy in high fat diet–fed mice was also described by Liu et al, using volume

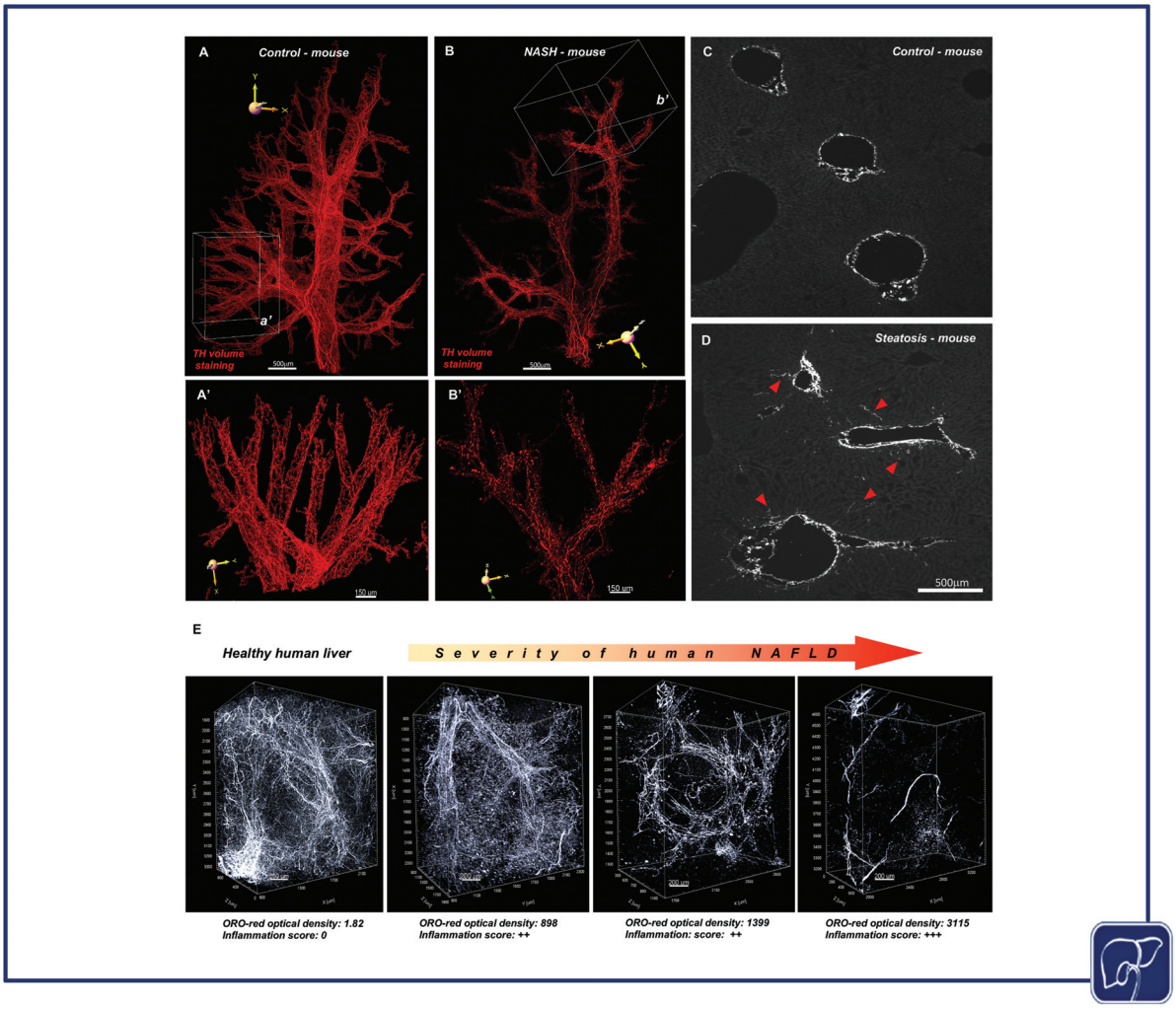


Fig. 2 Sympathetic nerve pathology in experimental and human nonalcoholic fatty liver disease (NAFLD). (**A, B**) tyrosine hydroxylase (TH) volume immunostaining in control mouse liver (A–A′) and in experimental steatohepatitis (B–B′). Boxes in A and B indicated with a′ and b′ are enlarged in A′ and B′, respectively. Note the extensive fiber degeneration in NASH. TH immunostaining in control mouse (**C**) and in experimental steatosis (**D**). Note the ectopic, parenchymal sprouting of noradrenergic fibers in steatosis (*arrowheads* in **D**). (**E**) Sympathetic nerve pathology in human NAFLD. Intraparenchymal fine fibers are gradually degenerating and disappearing with the more severe NAFLD pathology. ORO-red: Oil Red O lipid staining. (Micrographs are from Adori et al,[22] with slight modifications.)

imaging technique. The neuropathy was shown as a result of elevated macrophage-derived tumor necrosis factor α (TNFα) signaling through *sarm1*. The authors demonstrated that fiber dystrophy can be reversed by calorie restriction or by neutralizing TNFα antibody treatment. However, no comparison with NAFLD spectrum pathology was presented.[23]

We also described decrease in several adrenergic receptor and CX32 gap junction protein transcript levels already in steatotic mice fed with Western (high fat and high carbohydrate) diet, which may be a physiological response to the chronically high sympathetic tone. These expressions were further decreased in the steatohepatitis phase.[22] However, Wang et al found increased hepatic β3 mRNA and protein expression in rats fed with a high fat diet.[87]

Detailed Consequences of Hepatic Nerve Structural and Functional Impairments in NAFLD

Role in Altered Lipid Metabolism—Steatosis

A healthy liver normally stores minimal amounts of lipids. However, hepatocytes accumulate large amounts of fat with the progression of NAFLD. The fat content of hepatocytes is balanced by free fatty acid (FFA) uptake, de novo lipogenesis, hepatic β-oxidation, and triglyceride disposal (released as very low density lipoprotein [VLDL]).[88] The unbalance between the afore processes, such as increased lipid intake (FFA uptake or de novo lipogenesis) and/or decreased removal (impaired β-oxidation or VLDL secretion), leads to steatosis.

As we discussed earlier, NAFLD is characterized by a chronically high sympathetic tone. Elimination of liver

sympathetic nerves reduced FFA uptake and de novo lipogenesis, and reversed high fat diet-induced liver steatosis in mice. In contrast, no significant effect was noticed in VLDL release or β-oxidation.[20] Other studies in other models, however, found that sympathetic overactivity increased hepatic VLDL production in fa/fa Zucker rats, and liver sympathetic denervation decreased the VLDL secretion.[70,89] On the molecular level, sympathetic denervation decreases the mitochondrial carnitine palmitoyltransferase (CPT I-II) activities. These transporters are responsible for transferring long-chain fatty acids into mitochondria for β-oxidation.[90]

Regarding pharmacological studies targeting adrenoreceptors, more studies report increased hepatic β-receptor-mediated signaling during aging, as mediator of increasing hepatic steatosis.[91–93] However, interestingly, chronic treatment with β3 agonist decreased high fat diet-induced liver steatosis and inflammation in mice.[87] In another study, α-receptor agonist, but not β-receptor agonist, reduced steatosis in mice kept on a high fat diet, by stimulating fatty acid oxidation and autophagy.[21] Using primary rat hepatocytes and human hepatoma cells, Schott et al found that treatment with the β-receptor agonist isoproterenol caused substantial lipid droplet loss via activation of cytosolic adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), indicating a β-adrenoreceptor-dependent lipolysis pathway in hepatocytes. β-Adrenergic stimulation rapidly activated the protein kinase A, which led to the phosphorylation of ATGL and HSL, and their recruitment to the lipid droplet surfaces.[94] Genetic depletion of β2 receptor could aggravate high fat diet-induced liver lipid accumulation and liver injury in mice. Namely, β2-depletion significantly activated PPARg/CD36 signaling via inactivation of the cAMP response element-binding (CREB) protein to facilitate hepatocellular lipid deposition in mice kept on a hypercaloric diet.[95]

In the case of chronic consumption of high amount of fat, vagus-derived lipid sensing in the portal vein wall is likely an important mediator in the development of steatosis. Since the absorbed substance concentration is four to five times higher in the portal vein, compared with other parts of the circulatory system, the portal vein is an ideal predictor of systemic blood substance concentration.[14,96,97] Portal infusion of lipids significantly increases the hepatic vagal afferent nerve traffic.[98] Furthermore, the vagal afferent pathway influences neuronal activity in the rostral ventrolateral medulla, contributing to the chronic sympatho-excitation.[99] Another study showed that excessive portal venous supply of long-chain fatty acids in rat contributed to the development of insulin resistance via activation of the HPA axis and the sympathetic nervous system (SNS).[100]

Besides, vagal efferents may influence steatosis. A recent study describes that leptin injection into the mouse brain third ventricle, or stereotaxic leptin injection into the dorsal vagus complex in the medulla, decreases hepatic triglyceride content and protect from steatosis by increasing hepatic VLDL secretion and by suppressing de novo lipogenesis, independently from calorie intake. Cutting the hepatic branch of the vagus abrogates this effect, suggesting that the efferent vagus nerve conveys the leptin signal from the brain to the liver.[101] In a randomized placebo-controlled crossover trial with a limited number of participants ($n = 9–13$), single metreleptin (recombinant human leptin) injection stimulated hepatic VLDL secretion and reduced hepatic lipid content. However, in contrast to the previous preclinical study, metreleptin was peripherally (subcutaneously) administered to the participants. Applying the "modified sham feeding" technique of vagus stimulus in humans, the authors observed an increase in VLDL secretion, mimicking metreleptin effects.[102]

Role in Inflammation—Steatohepatitis

Approximately one-third of steatosis cases progress to steatohepatitis over the time. NASH inflammation is largely a consequence of chronically elevated FFA, free cholesterol, and oxidized cholesterol metabolites within the hepatocytes, which generates reactive oxidative species (ROS). This intracellular lipotoxic environment induces mitochondrial dysfunction and endoplasmic reticulum stress, which further escalate a ROS cascade, leading to irreversible hepatocyte damage and ultimately cell death.[103] This triggers a feed-forward loop between tissue injury and inflammation.

NASH inflammation is characterized by the activation of the innate immune system. Prominent players in this process are the liver-resident macrophage Kupffer cells, which compose 80 to 90% of all colonized macrophages in the human body.[104] Normally, Kupffer cells exhibit an M2-like activation phenotype and are involved in tissue repair and phagocytosis of cellular debris. However, in response to hepatocyte damage, Kupffer cells polarize toward proinflammatory M1 phenotype, secreting proinflammatory cytokines such as TNFα, IL-1b, IL-6, IL-8, and IL-12, thereby recruiting T-lymphocytes, natural killer T (NKT) cells, neutrophils, and blood-derived monocytes to the liver.[7,104–106] NKT cells are components of the innate immune system. They accumulate in the liver and regulate local proinflammatory (T helper 1) and anti-inflammatory (T helper 2) cytokine production.[107] Moreover, recruited NKT cells release perforin and granules, escalating liver damage.

Within the liver sinusoid, M1 Kupffer cells interact with other immune cells such as T cells, dendritic cells, and innate lymphocytes. Activation of Kupffer cells is a central event in triggering further liver injury. Namely, activated Kupffer cells are principal sources of further ROS production.[108] Their TNFα secretion contributes to hepatocyte apoptosis.[106] Moreover, M1 Kupffer cells release transforming growth factor β (TGF-β) and other profibrogenic cytokines, which will activate HCSs.[109] Accordingly, experimental depletion of Kupffer cells attenuates inflammation in mice kept on methionine/choline-deficient (MCD) or choline-deficient, L-amino acid-defined (CDAA) diets.[110–112]

Finally, it is interesting to mention that while NASH inflammation is generally considered as a sterile inflammation (i.e., inflammatory response in the absence of external antigen), accumulating data suggest that pathogen-associated molecular patterns in case of gastrointestinal dysbiosis may also exacerbate or even provoke the liver innate immune system response in NAFLD.[113] Namely, in patients with fatty liver, an increased gut barrier permeability develops.[114]

Microbial molecular structures like lipopolysaccharides, lipoteichoic acid, peptidoglycan, lipoglycans, and lipopeptides are recognized by toll-like receptors that are expressed by HSCs and by a wide variety of liver innate immune cells. Toll-like receptor activation then leads to the expression and release of several proinflammatory cytokines in these cells.[113]

As mentioned earlier, fine intraparenchymal noradrenergic fibers in the Disse space form neuroeffector junctions with Kupffer cells in humans and in nonhuman primates, and Kupffer cells express all the nine noradrenergic receptors, which overall suggest a robust sympathetic control of these macrophages. For instance, SNS promotes hepatocarcinogenesis by activating α1 receptors and facilitating proinflammatory environment in Kupffer cells. Inhibition of SNS reduces IL-6 and TGF-β expression, which suppresses hepatocarcinogenesis.[56] Moreover, Kupffer cell proinflammatory cytokine secretion (TNFα, IL-1b, IL-6) is potentiated by gut-derived noradrenaline release in sepsis.[115]

Regarding the context of NAFLD spectrum, the leptin-deficient Ob/Ob mice, characterized by obesity and fatty liver, showed elevated hepatic TNFα expression, and treatment with anti-TNF antibodies improved liver histology and reduced hepatic total fatty acid content.[116] Interestingly, Ob/Ob mice exhibit reduced noradrenaline level, due to a lower rate of noradrenaline synthesis and metabolism.[117] This increases hepatic NKT cell apoptosis and depletes NKT cells. As a result of this, hepatic proinflammatory cytokine production is increasing, which sensitizes lipotoxicity in the fatty liver. Noradrenaline treatment reduces NKT cell apoptosis and reduces hepatic inflammation in Ob/Ob mice.[118] The hepatic sympathetic neuropathy in mice kept in a high fat diet was mediated by TNFα derived from $CD11b^{+}$ $F4/80^{+}$ immune cells (Kupffer cells, macrophages).[23] In another recent study, 4-week administration of the β3 agonist BRL37344 attenuated lobular inflammation (the number of inflammation foci) in high fat diet-fed mice.[87]

The vagus nerve is also supposed to regulate hepatic inflammation in NASH, via α7 nicotinic cholinergic receptors on Kupffer cells. α7 knockout mice on MCD diet developed NASH faster than control mice, with highly activated Kupffer cells. Moreover, hepatic vagotomy aggravated the diet-induced NASH.[119] Furthermore, stimulation of the cervical trunk of the vagus nerve in mice increases the phagocytosis activity of Kupffer cells.[120]

Finally, we should also emphasize the role of HSCs in proinflammatory actions in injured liver. Namely, noradrenaline stimulates the secretion of inflammatory chemokines (RANTES and interleukin-8) in a dose-dependent manner, and triggers NF-kappaB activation in HSCs in vitro.[55]

Role in Hepatic Regeneration and Fibrosis in NAFLD

SNS regulates liver repair by modulating HSCs (main fibrogenic cells in liver) and hepatic progenitor cells (HPCs).

The resident HPCs help regenerate the epithelial compartment after severe liver injury. The number of HPCs has been found to be increased in NAFLD.[121] In general, noradrenaline and adrenoreceptor agonists stimulate the proliferation of cholangiocytes.[61,62] Moreover, the β-receptor agonist isoproterenol promoted recovery of the HPC pool in dopamine β-hydroxylase (DBH)-deficient mice after acetaminophen-induced liver injury.[122] Contrary, in an earlier study, the number of HPCs was increased after chemical sympathectomy by 6-hydroxydopamine (6-OHDA).[65]

HSCs (or perisinusoidal cells or Ito-cells; with older terminology: lipocytes or fat-storing cells) are composed of one-third of nonparenchymal cells and 8% of all cells in the mammalian liver.[123] With "dendritic-like" processes, they form direct contacts with sinusoidal endothelial cells, hepatocytes, and Kupffer cells, which promote intercellular crosstalk and transport of soluble mediators among these cell types.[124] Moreover, HSCs are neuroglia-like cells,[125] expressing noradrenaline synthetizing enzymes,[53,65] acetylcholine synthesizing enzymes, most adrenoreceptors, glial fibrillary acidic protein, neural cell adhesion molecule, and synaptophysin.[66,125–127] HSCs release noradrenaline and adrenaline in human primary cell culture[54] and murine HSC lysates contain dopamine, serotonin, and catecholamine metabolites.[53] A recent study, however, using single-cell RNA sequencing has reported that only a subpopulation of HSCs has the gene expression signature of noradrenaline synthesis, pointing to the heterogeneity of these cells.[128] ELMI studies confirmed that HSCs, just like Kupffer cells, are innervated by fine noradrenergic fibers.[37]

In fibrosis, HSCs from quiescent phenotype move to an activated, myofibroblastic phenotype. They release hepatic growth factor that promotes hepatocyte proliferation and maintenance.[129] They also express alpha smooth muscle actin (αSMA) and fibrogenic matrix proteins.[130] Activation of HCSs is originally part of a regenerating process, which, in the long term, may turn to fibrosis and then ultimately to cirrhosis, due to inadequate communication between HCSs and neighboring cells.[131]

Exogenous noradrenaline dose-dependently increases the proliferation and collagen expression of activated HSCs. Activated HCSs in human primary culture upregulate a/b adrenoceptors as well.[54,132] Injury-related fibrogenic response was inhibited in DBH knockout mice, evidenced by reduced expression of αSMA, decreased induction of TGF-β1, and collagen in cultured HCSs from DBH knockout animals.[53] Moreover, Ob/Ob mice with low catecholamine level and lower SNS tone are resistant to liver fibrosis,[133] and chemical sympathectomy or α1 receptor antagonism inhibits carbon-tetrachloride (CCl4)-induced liver fibrosis in rats.[134] Overall, activation of liver noradrenergic (sympathetic) nerves exacerbates liver fibrosis, while sympathetic inhibition attenuates it.

Importantly, acetylcholine also facilitates HSCs proliferation via intracellular activation of phosphoinositide 3-kinase and MEK cell survival pathway, and induces TGF-β and collagen fibrogenesis via M2 and M3 receptors.[66]

Role in Hepatic Hemodynamics in NAFLD

Portal hypertension (PH; supraphysiological pressure in the portal venous system) is a severe complication in liver cirrhosis.[135] The pathophysiology of PH involves both

hepatic factors (increased intrahepatic resistance to portal venous and sinusoidal blood flow) and/or extrahepatic effects (splanchnic arterial vasodilation).[135,136] Although PH has mostly been discussed in the context of cirrhosis, elevated portal venous pressure has also been detected in earlier phases of NAFLD, when fibrosis is less advanced, and cirrhosis is absent.[136,137]

Numerous earlier studies reported decreased hepatic blood flow and increased hepatic arterial and portal venous pressure after electrical stimulation of the hepatic nerves in rat,[138] dog,[139] or cat.[140] Moreover, electrical stimulation of portal vein-associated nerves elicited α-receptor-mediated constriction of portal venules, sinusoids, and hepatic arteries, but no response could be recorded from the central vein.[58] Intraportal injection of 6-OHDA prevented the large reduction of hepatic blood volume normally seen with nerve stimulation, while the contractive response to noradrenaline infusion was not altered.[141] In a rat study, repetitive periportal nerve stimulation was accompanied with a gradually diminished noradrenaline overflow, while the metabolic (glucose output) and hemodynamic (portal vein contraction) effects remained unchanged,[142] possibly indicating an adrenergic receptor sensitization during repeated stimulation. While β1–2 adrenoreceptors have vasoconstrictor effects, β3 is a vasodilator receptor. β3 agonist treatment in rats significantly and dose-dependently caused portal vein (but not central vein) relaxation and decreased portal pressure in cirrhosis (induced by CCl4), but not in controls.[60]

Early investigations showed a direct relation between the size of portal/sinusoid pressure and circulating level of noradrenaline in cirrhosis.[143] Based on advanced 3D imaging, we recently described and quantitatively characterized a portal vein stenotic alteration (abnormal narrowing) in mouse experimental steatohepatitis. Systematic 3D analysis revealed that such portal stenosis ended exactly where the already degenerating noradrenergic innervations terminated, followed by dilated distal portal branches (►**Fig. 3A,B**). At the same time, the central vein system that virtually lacks innervation did not show decreased volume or shrunken morphology. These findings propose that the liver periportal sympathetic nerves could contribute to a stenotic portal vein condition in advanced stages of NAFLD.[22] The latter results also suggest that these morphologically impaired sympathetic fibers in NASH are still in operation, albeit presumably with impaired functionality. Taken together with the well-established chronically high sympathetic tone in NAFLD, a potential role of periportal sympathetic nerves in the development of PH is suggested.

Furthermore, HSCs are extensively involved in the regulation of hepatic sinusoidal microcirculation by contraction and relaxation.[144] In PH, resistance of the sinusoidal wall is increasing, leading to a decreased microcirculation. Thus, HSCs proliferation and increased contractility may also contribute to PH,[145] and noradrenergic signaling may serve as a significant factor in such process.[144]

Finally, increased portal/sinusoid pressure leads to further activation of sympathetic nerves in heart and kidney, which is mediated by activation of non–volume-dependent hepatic baroreceptors.[146]

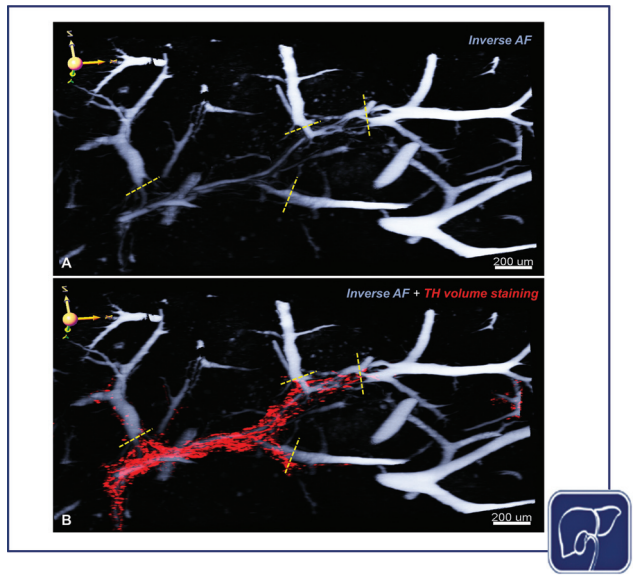


Fig. 3 Portal vein stenosis in experimental steatohepatitis and its spatial correlation with the remaining sympathetic nerves. (**A, B**) Liver vasculature in steatohepatitic mouse is visualized by inverted autofluorescence (AF) in 3D (*gray channel* in **A** and **B**). Portal vein stenotic alteration is correlating with the extension of the already degenerating noradrenergic nerve fibers (tyrosine hydroxylase [TH] volume immunostaining, *red channel* in B). *Yellow dashed lines* indicate the end of TH^+ innervations. (Micrographs are from Adori et al.[22])

Summary and Concluding Remarks

Accumulating evidence suggests that hepatic innervations have multiple roles in the pathomechanism of NAFLD. Major players are supposed to be the efferent sympathetic (noradrenergic) nerves, affecting the development/progression of steatosis, inflammation, fibrosis, and liver hemodynamical alterations. Sympathetic nerve effects on the liver are overwhelmingly complex and lots of details are still poorly understood.

Namely, while chronically high sympathetic tone seems to drive liver steatosis, more studies have shown that β-adrenoreceptor agonists actually protect against steatosis in experimental NAFLD. The extensive interaction between sympathetic innervation and Kupffer cells is doubtless, but it needs further exploration in the context of steatohepatitis. Here, the *balance* between proinflammatory M1 Kupffer cells and anti-inflammatory M2 Kupffer cells is likely crucial to regulate the occurrence and development of liver inflammation and subsequent injury.[147] Accordingly, limiting the amount of M1 Kupffer cells and promoting M2 Kupffer cell polarization may be a valuable therapeutic strategy in attenuating inflammation in NAFLD. Activation of various subsets of adrenergic receptors seems to produce antagonistic effects on monocytes. Namely, α-receptors are both pro- and anti-inflammatory, while β-adrenergic receptors mostly show

immunosuppressive and anti-inflammatory properties.[148,149] Finally, based on the available data, sympathetic nerve stimuli in NAFLD are clearly profibrotic with promoting HSC activation to myofibroblastic phenotype, and mostly vasoconstrictor, albeit β3 receptors have vasodilator effects in mice.

As discussed in this review, several noradrenergic receptors have been described in hepatocytes, cholangiocytes, and in the wall of portal vessels. Moreover, virtually all noradrenergic receptors are expressed by Kupffer cells and HCSs. In a healthy liver, orchestration of noradrenergic receptors by the sympathetic nerves maintains equilibrium in several signaling mechanisms with sometimes antagonistic effects, which overall promotes liver metabolic homeostasis. These fine-tuned balances may slowly change under metabolic stress and/or with altered nerve functionality. Specifically, in NAFLD, chronically high sympathetic tone may lead to alterations in receptor expression levels, in receptor sensitivity, and perhaps in signal transduction cascades, with a cell-autonomous spatial-temporal character. Besides, increased plasticity (disorganization, ectopic sprouting, and mild trimming) of liver sympathetic nerves in earlier phase of the disease (steatosis), and degeneration of sympathetic nerves in more advanced stages (steatohepatitis), have been described in NAFLD. These structural alterations likely come along with impaired nerve functionality and lack of adequate signaling, which further affect the receptors, as a vicious cycle of hepatic noradrenergic pathology. All these may contribute to a multiphase hepatic "catecholamine resistance" (inability of (nor)adrenaline to induce a defined response),[150] which should be considered when planning and evaluating pharmacological studies or pharmacotherapeutic strategies targeting the SNS in NAFLD.

Afferent vagal nerves also seem to be significant in the pathomechanism of NAFLD. Specifically, lipid sensing by vagal afferent fibers in the portal vein wall is likely an important player in the development of steatosis by influencing neuronal activity in the ventrolateral medulla and, consequently, by contributing to the chronic sympathoexcitation.

Future Perspectives

In an interesting recent study, Wang et al reported that sustained sleep deprivation promotes hepatic steatosis, which is mediated by sympathetic overactivation.[151] Other studies also found that short sleep duration is a risk of incident NAFLD.[152,153] Considering that sleep deprivation, poor sleep quality, and stressful lifestyle are very common in modern societies, their metabolic consequences that possibly imply hepatic steatosis due to elevated sympathetic tone may need further investigations.

Also, despite its high importance, only a few studies explored the development and integrity of hepatic nerves of offspring in case of maternal obesity or perinatal/early postnatal high fat nutrition.[82] More information may be needed in this highly relevant field, since a potential early abnormal hepatic nerve development may have long-lasting consequences, particularly in the case of metabolic challenges later in life.

Numerous studies examined parasympathetic nerve effects on the liver by hepatic vagotomy experiments. However, as emphasized by Berthoud, cutting the common hepatic vagal branch denervates not only the liver but also parts of the distal stomach, pylorus, duodenum, and pancreas.[40] Moreover, common hepatic branch vagotomy not only destroys vagal fibers, since approximately 30% of the nerve fibers running in this branch are of nonvagal origin.[154] As mentioned earlier, we and others failed to detect parasympathetic (cholinergic) nerves in rodent, nonhuman primate, and human livers by using volume imaging.[22,23] However, cholinergic fibers were described around the liver hilum with tracing studies, and some authors speculate that parasympathetic nerves may act on the liver indirectly, by innervating hilar sympathetic nerve structures.[45] Overall, more detailed and comparative anatomical studies are needed concerning the parasympathetic liver innervations.

The pathogenesis of NAFLD is incompletely understood. Currently, the therapeutic options are limited to lifestyle changes and no approved drug therapy exists that may address both the progression of liver fibrosis and associated metabolic disturbances in NAFLD.[155]

Hepatic nerves, primarily the efferent sympathetic (noradrenergic) nerves, have multiple subtle regulatory roles in liver glucose and lipid metabolism, bile secretion, inflammatory reaction, hemodynamics, and regeneration. However, their role may be more essential during the fight-or-flight response or when subjected to metabolic challenges, like in the case of NAFLD.[156] Future studies, simultaneously considering structural and functional alterations of hepatic nerves and their receptors, may reveal novel aspects in the pathophysiology of NAFLD, which could ultimately lead to pharmacotherapeutic advances.

Conflict of Interest
None declared.

Acknowledgments
We are grateful to Dr. Ewa Ellis (Karolinska Institutet, Department of Clinical Science, Intervention and Technology) and to Dr. Elisabeth Verboven (Karolinska Institutet, Department of Cell and Molecular Biology) for critical reading of the manuscript and for valuable comments, as well as to Nupur Sharma, Department of Molecular and Cellular Medicine, Institute of Liver and Biliary Sciences, New Delhi, India, for the valuable help in literature search. The Graphical Abstract was prepared with the application of the online software BioRender. Figures 1 to 3 are from/modified from: Adori C. et al., Sci. Adv. 7, eabg5733 (2021).

References

1 Kaya E, Yılmaz Y. Non-alcoholic fatty liver disease: a growing public health problem in Turkey. Turk J Gastroenterol 2019;30 (10):865–871
2 Younossi ZM. Non-alcoholic fatty liver disease - a global public health perspective. J Hepatol 2019;70(03):531–544
3 Yeh MM, Brunt EM. Pathology of nonalcoholic fatty liver disease. Am J Clin Pathol 2007;128(05):837–847
4 Stefan N, Cusi K. A global view of the interplay between non-alcoholic fatty liver disease and diabetes. Lancet Diabetes Endocrinol 2022;10(04):284–296
5 Mantovani A, Scorletti E, Mosca A, Alisi A, Byrne CD, Targher G. Complications, morbidity and mortality of nonalcoholic fatty liver disease. Metabolism 2020;111S:154170
6 Mantovani A, Csermely A, Petracca G, et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2021;6(11):903–913
7 Ibrahim SH, Hirsova P, Gores GJ. Non-alcoholic steatohepatitis pathogenesis: sublethal hepatocyte injury as a driver of liver inflammation. Gut 2018;67(05):963–972
8 Diehl AM, Day C. Cause, pathogenesis, and treatment of nonalcoholic steatohepatitis. N Engl J Med 2017;377(21):2063–2072
9 Takahashi Y, Fukusato T. Histopathology of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. World J Gastroenterol 2014;20(42):15539–15548
10 Lau JK, Zhang X, Yu J. Animal models of non-alcoholic fatty liver disease: current perspectives and recent advances. J Pathol 2017; 241(01):36–44
11 Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol 2020;73(01):202–209
12 Mizuno K, Ueno Y. Autonomic nervous system and the liver. Hepatol Res 2017;47(02):160–165
13 Streba LA, Vere CC, Ionescu AG, Streba CT, Rogoveanu I. Role of intrahepatic innervation in regulating the activity of liver cells. World J Hepatol 2014;6(03):137–143
14 Jensen KJ, Alpini G, Glaser S. Hepatic nervous system and neurobiology of the liver. Compr Physiol 2013;3(02):655–665
15 Amir M, Yu M, He P, Srinivasan S. Hepatic autonomic nervous system and neurotrophic factors regulate the pathogenesis and progression of non-alcoholic fatty liver disease. Front Med (Lausanne) 2020;7:62
16 Kandilis AN, Papadopoulou IP, Koskinas J, Sotiropoulos G, Tiniakos DG. Liver innervation and hepatic function: new insights. J Surg Res 2015;194(02):511–519
17 Colle I, Van Vlierberghe H, Troisi R, De Hemptinne B. Transplanted liver: consequences of denervation for liver functions. Anat Rec A Discov Mol Cell Evol Biol 2004;280(01):924–931
18 Laryea M, Watt KD, Molinari M, et al. Metabolic syndrome in liver transplant recipients: prevalence and association with major vascular events. Liver Transpl 2007;13(08):1109–1114
19 Schneiter P, Gillet M, Chioléro R, et al. Mechanisms of postprandial hyperglycemia in liver transplant recipients: comparison of liver transplant patients with kidney transplant patients and healthy controls. Diabetes Metab 2000;26(01):51–56
20 Hurr C, Simonyan H, Morgan DA, Rahmouni K, Young CN. Liver sympathetic denervation reverses obesity-induced hepatic steatosis. J Physiol 2019;597(17):4565–4580
21 Nakade Y, Kitano R, Yamauchi T, et al. Effect of adrenergic agonists on high-fat diet-induced hepatic steatosis in mice. Int J Mol Sci 2020;21(24):21
22 Adori C, Daraio T, Kuiper R, et al. Disorganization and degeneration of liver sympathetic innervations in nonalcoholic fatty liver disease revealed by 3D imaging. Sci Adv 2021;7(30):7
23 Liu K, Yang L, Wang G, et al. Metabolic stress drives sympathetic neuropathy within the liver. Cell Metab 2021;33(03):666–675. e4
24 Galen C. On the Usefulness of the Parts of the Body. May MT tr. New York: Cornell University Press; 1968
25 Pfülger E. Über die Abhängigkeit der Leber von dem Nervensystem. Arch Gesamte Physiol Mens Tiere (Pfluegers) 1869; 2:459–491. Accessed on April 17, 2023, at: https://link.springer.com/article/10.1007/BF01628420#citeas
26 Delalande JM, Milla PJ, Burns AJ. Hepatic nervous system development. Anat Rec A Discov Mol Cell Evol Biol 2004;280(01): 848–853
27 Ding WG, Kitasato H, Kimura H. Development of neuropeptide Y innervation in the liver. Microsc Res Tech 1997;39(04):365–371
28 Tanimizu N, Ichinohe N, Mitaka T. Intrahepatic bile ducts guide establishment of the intrahepatic nerve network in developing and regenerating mouse liver. Development 2018;145(09):145
29 Koike N, Tadokoro T, Ueno Y, et al. Development of the nervous system in mouse liver. World J Hepatol 2022;14(02):386–399
30 Tiniakos DG, Mathew J, Kittas C, Burt AD. Ontogeny of human intrahepatic innervation. Virchows Arch 2008;452(04):435–442
31 Shimazu T. Neuronal regulation of hepatic glucose metabolism in mammals. Diabetes Metab Rev 1987;3(01):185–206
32 Shimazu T. Innervation of the liver and glucoregulation: roles of the hypothalamus and autonomic nerves. Nutrition 1996;12 (01):65–66
33 Burt AD, Tiniakos D, MacSween RN, Griffiths MR, Wisse E, Polak JM. Localization of adrenergic and neuropeptide tyrosine-containing nerves in the mammalian liver. Hepatology 1989;9(06): 839–845
34 Miller BM, Oderberg IM, Goessling W. Hepatic nervous system in development, regeneration, and disease. Hepatology 2021;74 (06):3513–3522
35 Lin YS, Nosaka S, Amakata Y, Maeda T. Comparative study of the mammalian liver innervation: an immunohistochemical study of protein gene product 9.5, dopamine beta-hydroxylase and tyrosine hydroxylase. Comp Biochem Physiol Part A Physiol 1995;110(04):289–298
36 Akiyoshi H, Gonda T, Terada T. A comparative histochemical and immunohistochemical study of aminergic, cholinergic and peptidergic innervation in rat, hamster, guinea pig, dog and human livers. Liver 1998;18(05):352–359
37 Forssmann WG, Ito S. Hepatocyte innervation in primates. J Cell Biol 1977;74(01):299–313
38 Nobin A, Baumgarten HG, Falck B, Ingemansson S, Moghimzadeh E, Rosengren E. Organization of the sympathetic innervation in liver tissue from monkey and man. Cell Tissue Res 1978;195(03): 371–380
39 Mundinger TO, Verchere CB, Baskin DG, Boyle MR, Kowalyk S, Taborsky GJ Jr. Galanin is localized in sympathetic neurons of the dog liver. Am J Physiol 1997;273(06):E1194–E1202
40 Berthoud HR. Anatomy and function of sensory hepatic nerves. Anat Rec A Discov Mol Cell Evol Biol 2004;280(01):827–835
41 Berthoud HR, Kressel M, Neuhuber WL. An anterograde tracing study of the vagal innervation of rat liver, portal vein and biliary system. Anat Embryol (Berl) 1992;186(05):431–442
42 Amenta F, Cavallotti C, Ferrante F, Tonelli F. Cholinergic nerves in the human liver. Histochem J 1981;13(03):419–424
43 Schäfer MK, Eiden LE, Weihe E. Cholinergic neurons and terminal fields revealed by immunohistochemistry for the vesicular acetylcholine transporter. II. The peripheral nervous system. Neuroscience 1998;84(02):361–376
44 Berthoud HR, Neuhuber WL. Vagal mechanisms as neuromodulatory targets for the treatment of metabolic disease. Ann N Y Acad Sci 2019;1454(01):42–55
45 Berthoud HR, Powley TL. Characterization of vagal innervation to the rat celiac, suprarenal and mesenteric ganglia. J Auton Nerv Syst 1993;42(02):153–169
46 Uyama N, Geerts A, Reynaert H. Neural connections between the hypothalamus and the liver. Anat Rec A Discov Mol Cell Evol Biol 2004;280(01):808–820

47 Seseke FG, Gardemann A, Jungermann K. Signal propagation via gap junctions, a key step in the regulation of liver metabolism by the sympathetic hepatic nerves. FEBS Lett 1992;301(03): 265–270
48 Miyashita T, Takeda A, Iwai M, Shimazu T. Single administration of hepatotoxic chemicals transiently decreases the gap-junction-protein levels of connexin 32 in rat liver. Eur J Biochem 1991;196(01):37–42
49 Temme A, Stümpel F, Söhl G, et al. Dilated bile canaliculi and attenuated decrease of nerve-dependent bile secretion in connexin32-deficient mouse liver. Pflugers Arch 2001;442(06): 961–966
50 McKee C, Soeda J, Asilmaz E, et al. Propranolol, a β-adrenoceptor antagonist, worsens liver injury in a model of non-alcoholic steatohepatitis. Biochem Biophys Res Commun 2013;437(04): 597–602
51 Kajiyama Y, Ui M. Switching from alpha 1- to beta-subtypes in adrenergic response during primary culture of adult-rat hepatocytes as affected by the cell-to-cell interaction through plasma membranes. Biochem J 1994;303(Pt 1):313–321
52 Tao X, Chen C, Chen Y, et al. β_2-adrenergic receptor promotes liver regeneration partially through crosstalk with c-met. Cell Death Dis 2022;13(06):571
53 Oben JA, Roskams T, Yang S, et al. Hepatic fibrogenesis requires sympathetic neurotransmitters. Gut 2004;53(03):438–445
54 Sigala B, McKee C, Soeda J, et al. Sympathetic nervous system catecholamines and neuropeptide Y neurotransmitters are upregulated in human NAFLD and modulate the fibrogenic function of hepatic stellate cells. PLoS One 2013;8(09):e72928
55 Sancho-Bru P, Bataller R, Colmenero J, et al. Norepinephrine induces calcium spikes and proinflammatory actions in human hepatic stellate cells. Am J Physiol Gastrointest Liver Physiol 2006;291(05):G877–G884
56 Huan HB, Wen XD, Chen XJ, et al. Sympathetic nervous system promotes hepatocarcinogenesis by modulating inflammation through activation of alpha1-adrenergic receptors of Kupffer cells. Brain Behav Immun 2017;59:118–134
57 Ko S, Russell JO, Molina LM, Monga SP. Liver progenitors and adult cell plasticity in hepatic injury and repair: knowns and unknowns. Annu Rev Pathol 2020;15:23–50
58 Reilly FD, McCuskey RS, Cilento EV. Hepatic microvascular regulatory mechanisms. I. Adrenergic mechanisms. Microvasc Res 1981;21(01):103–116
59 Huang YT, Lin LC, Chern JW, Lin HC, Hong CY. Portal hypotensive effects of combined terlipressin and DL-028, a synthetic alpha 1 adrenoceptor antagonist administration on anesthetized portal hypertensive rats. Liver 1999;19(02):129–134
60 Vasina V, Giannone F, Domenicali M, et al. Portal hypertension and liver cirrhosis in rats: effect of the β3-adrenoceptor agonist SR58611A. Br J Pharmacol 2012;167(05):1137–1147
61 Alpini G, Franchitto A, Demorrow S, et al. Activation of alpha(1) -adrenergic receptors stimulate the growth of small mouse cholangiocytes via calcium-dependent activation of nuclear factor of activated T cells 2 and specificity protein 1. Hepatology 2011;53(02):628–639
62 Glaser S, Alvaro D, Francis H, et al. Adrenergic receptor agonists prevent bile duct injury induced by adrenergic denervation by increased cAMP levels and activation of Akt. Am J Physiol Gastrointest Liver Physiol 2006;290(04):G813–G826
63 Aizarani N, Saviano A, Sagar, et al. A human liver cell atlas reveals heterogeneity and epithelial progenitors. Nature 2019;572 (7768):199–204
64 Lelou E, Corlu A, Nesseler N, et al. The role of catecholamines in pathophysiological liver processes. Cells 2022;11(06):11
65 Oben JA, Roskams T, Yang S, et al. Sympathetic nervous system inhibition increases hepatic progenitors and reduces liver injury. Hepatology 2003;38(03):664–673
66 Morgan ML, Sigala B, Soeda J, et al. Acetylcholine induces fibrogenic effects via M2/M3 acetylcholine receptors in non-alcoholic steatohepatitis and in primary human hepatic stellate cells. J Gastroenterol Hepatol 2016;31(02):475–483
67 Lechner SG, Markworth S, Poole K, et al. The molecular and cellular identity of peripheral osmoreceptors. Neuron 2011;69 (02):332–344
68 Sabath E, Báez-Ruiz A, Buijs RM. Non-alcoholic fatty liver disease as a consequence of autonomic imbalance and circadian desynchronization. Obes Rev 2015;16(10):871–882
69 Licht CM, Vreeburg SA, van Reedt Dortland AK, et al. Increased sympathetic and decreased parasympathetic activity rather than changes in hypothalamic-pituitary-adrenal axis activity is associated with metabolic abnormalities. J Clin Endocrinol Metab 2010;95(05):2458–2466
70 Bruinstroop E, Eliveld J, Foppen E, et al. Hepatic denervation and dyslipidemia in obese Zucker (fa/fa) rats. Int J Obes 2015;39(11): 1655–1658
71 Gao H, Molinas AJR, Miyata K, Qiao X, Zsombok A. Overactivity of liver-related neurons in the paraventricular nucleus of the hypothalamus: electrophysiological findings in *db/db* mice. J Neurosci 2017;37(46):11140–11150
72 Menacho-Márquez M, Nogueiras R, Fabbiano S, et al. Chronic sympathoexcitation through loss of Vav3, a Rac1 activator, results in divergent effects on metabolic syndrome and obesity depending on diet. Cell Metab 2013;18(02):199–211
73 Jung I, Lee DY, Lee MY, et al. Autonomic imbalance increases the risk for non-alcoholic fatty liver disease. Front Endocrinol (Lausanne) 2021;12:752944
74 Targher G, Mantovani A, Grander C, et al. Association between non-alcoholic fatty liver disease and impaired cardiac sympathetic/parasympathetic balance in subjects with and without type 2 diabetes - the Cooperative Health Research in South Tyrol (CHRIS)-NAFLD sub-study. Nutr Metab Cardiovasc Dis 2021;31(12):3464–3473
75 Wider MD. Metabolic syndrome and the hepatorenal reflex. Surg Neurol Int 2016;7:99
76 Nam SW, Song HJ, Back SJ, et al. Decreased hepatic nerve fiber innervation in patients with liver cirrhosis. Gut Liver 2007;1 (02):165–170
77 Scoazec JY, Racine L, Couvelard A, et al. Parenchymal innervation of normal and cirrhotic human liver: a light and electron microscopic study using monoclonal antibodies against the neural cell-adhesion molecule. J Histochem Cytochem 1993;41 (06):899–908
78 Miyazawa Y, Fukuda Y, Imoto M, Koyama Y, Nagura H. Immunohistochemical studies on the distribution of nerve fibers in chronic liver diseases. Am J Gastroenterol 1988;83(10): 1108–1114
79 Lee JA, Ahmed Q, Hines JE, Burt AD. Disappearance of hepatic parenchymal nerves in human liver cirrhosis. Gut 1992;33(01): 87–91
80 Jaskiewicz K, Robson SC, Banach L. Toxic hepatic injury is associated with proliferation of portal nerve fibers. Pathol Res Pract 1993;189(10):1191–1194
81 Ueno T, Sata M, Sakata R, et al. Hepatic stellate cells and intralobular innervation in human liver cirrhosis. Hum Pathol 1997; 28(08):953–959
82 Grant WF, Nicol LE, Thorn SR, Grove KL, Friedman JE, Marks DL. Perinatal exposure to a high-fat diet is associated with reduced hepatic sympathetic innervation in one-year old male Japanese macaques. PLoS One 2012;7(10):e48119
83 Lin B, Ma Y, Wu S, Liu Y, Liu L, Wu L. Novel serum biomarkers for noninvasive diagnosis and screening of nonalcoholic fatty liver disease-related hepatic fibrosis. OMICS 2019;23(04):181–189
84 Ádori C, Glück L, Barde S, et al. Critical role of somatostatin receptor 2 in the vulnerability of the central noradrenergic

system: new aspects on Alzheimer's disease. Acta Neuropathol 2015;129(04):541–563
85 Adori C, Low P, Andó RD, et al. Ultrastructural characterization of tryptophan hydroxylase 2-specific cortical serotonergic fibers and dorsal raphe neuronal cell bodies after MDMA treatment in rat. Psychopharmacology (Berl) 2011;213(2-3):377–391
86 Adori C, Andó RD, Szekeres M, et al. Recovery and aging of serotonergic fibers after single and intermittent MDMA treatment in Dark Agouti rat. J Comp Neurol 2011;519(12): 2353–2378
87 Wang Z, Li S, Wang R, et al. The protective effects of the β3 adrenergic receptor agonist BRL37344 against liver steatosis and inflammation in a rat model of high-fat diet-induced nonalcoholic fatty liver disease (NAFLD). Mol Med 2020;26(01):54
88 Jou J, Choi SS, Diehl AM. Mechanisms of disease progression in nonalcoholic fatty liver disease. Semin Liver Dis 2008;28(04): 370–379
89 Tavares FL, Seelaender MC. Hepatic denervation impairs the assembly and secretion of VLDL-TAG. Cell Biochem Funct 2008;26(05):557–565
90 Carreño FR, Seelaender MC. Liver denervation affects hepatocyte mitochondrial fatty acid transport capacity. Cell Biochem Funct 2004;22(01):9–17
91 Shi Y, Pizzini J, Wang H, et al. **β_2**-Adrenergic receptor agonist induced hepatic steatosis in mice: modeling nonalcoholic fatty liver disease in hyperadrenergic states. Am J Physiol Endocrinol Metab 2021;321(01):E90–E104
92 Shi Y, Shu ZJ, Wang H, et al. Altered expression of hepatic β-adrenergic receptors in aging rats: implications for age-related metabolic dysfunction in liver. Am J Physiol Regul Integr Comp Physiol 2018;314(04):R574–R583
93 Shi Y, Shu ZJ, Xue X, Yeh CK, Katz MS, Kamat A. β2-Adrenergic receptor ablation modulates hepatic lipid accumulation and glucose tolerance in aging mice. Exp Gerontol 2016;78:32–38
94 Schott MB, Rasineni K, Weller SG, et al. β-Adrenergic induction of lipolysis in hepatocytes is inhibited by ethanol exposure. J Biol Chem 2017;292(28):11815–11828
95 Tao X, Hu Y, Li L, et al. Genetic deletion of β_2 adrenergic receptors exacerbates hepatocellular lipid accumulation in high-fat diet mice. Biochem Biophys Res Commun 2019;511(01):73–78
96 Cox JE, Kelm GR, Meller ST, Spraggins DS, Randich A. Truncal and hepatic vagotomy reduce suppression of feeding by jejunal lipid infusions. Physiol Behav 2004;81(01):29–36
97 Morita H, Abe C. Negative feedforward control of body fluid homeostasis by hepatorenal reflex. Hypertens Res 2011;34(08): 895–905
98 Randich A, Spraggins DS, Cox JE, Meller ST, Kelm GR. Jejunal or portal vein infusions of lipids increase hepatic vagal afferent activity. Neuroreport 2001;12(14):3101–3105
99 Lorenzo-Martín LF, Menacho-Márquez M, Fabbiano S, et al. Vagal afferents contribute to sympathoexcitation-driven metabolic dysfunctions. J Endocrinol 2019;240(03):483–496
100 Benthem L, Keizer K, Wiegman CH, et al; de Boer SF. Excess portal venous long-chain fatty acids induce syndrome X via HPA axis and sympathetic activation. Am J Physiol Endocrinol Metab 2000;279(06):E1286–E1293
101 Hackl MT, Fürnsinn C, Schuh CM, et al. Brain leptin reduces liver lipids by increasing hepatic triglyceride secretion and lowering lipogenesis. Nat Commun 2019;10(01):2717
102 Metz M, Beghini M, Wolf P, et al. Leptin increases hepatic triglyceride export via a vagal mechanism in humans. Cell Metab 2022;34(11):1719–1731.e5
103 Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. Hepatology 2010;52(05):1836–1846
104 Chen J, Deng X, Liu Y, et al. Kupffer cells in non-alcoholic fatty liver disease: friend or foe? Int J Biol Sci 2020;16(13): 2367–2378
105 Heymann F, Tacke F. Immunology in the liver – from homeostasis to disease. Nat Rev Gastroenterol Hepatol 2016;13(02):88–110
106 Alisi A, Carpino G, Oliveira FL, Panera N, Nobili V, Gaudio E. The role of tissue macrophage-mediated inflammation on NAFLD pathogenesis and its clinical implications. Mediators Inflamm 2017;2017:8162421
107 Benlagha K, Kyin T, Beavis A, Teyton L, Bendelac A. A thymic precursor to the NK T cell lineage. Science 2002;296 (5567):553–555
108 Clària J, González-Périz A, López-Vicario C, Rius B, Titos E. New insights into the role of macrophages in adipose tissue inflammation and fatty liver disease: modulation by endogenous omega-3 fatty acid-derived lipid mediators. Front Immunol 2011;2:49
109 Pradere JP, Kluwe J, De Minicis S, et al. Hepatic macrophages but not dendritic cells contribute to liver fibrosis by promoting the survival of activated hepatic stellate cells in mice. Hepatology 2013;58(04):1461–1473
110 Rivera CA, Adegboyega P, van Rooijen N, Tagalicud A, Allman M, Wallace M. Toll-like receptor-4 signaling and Kupffer cells play pivotal roles in the pathogenesis of non-alcoholic steatohepatitis. J Hepatol 2007;47(04):571–579
111 Miura K, Yang L, van Rooijen N, Ohnishi H, Seki E. Hepatic recruitment of macrophages promotes nonalcoholic steatohepatitis through CCR2. Am J Physiol Gastrointest Liver Physiol 2012;302(11):G1310–G1321
112 Tosello-Trampont AC, Landes SG, Nguyen V, Novobrantseva TI, Hahn YS. Kuppfer cells trigger nonalcoholic steatohepatitis development in diet-induced mouse model through tumor necrosis factor-α production. J Biol Chem 2012;287(48): 40161–40172
113 Park JW, Kim SE, Lee NY, et al. Role of microbiota-derived metabolites in alcoholic and non-alcoholic fatty liver diseases. Int J Mol Sci 2021;23(01):23
114 Imajo K, Fujita K, Yoneda M, et al. Hyperresponsivity to low-dose endotoxin during progression to nonalcoholic steatohepatitis is regulated by leptin-mediated signaling. Cell Metab 2012;16(01): 44–54
115 Yang S, Koo DJ, Zhou M, Chaudry IH, Wang P. Gut-derived norepinephrine plays a critical role in producing hepatocellular dysfunction during early sepsis. Am J Physiol Gastrointest Liver Physiol 2000;279(06):G1274–G1281
116 Li Z, Yang S, Lin H, et al. Probiotics and antibodies to TNF inhibit inflammatory activity and improve nonalcoholic fatty liver disease. Hepatology 2003;37(02):343–350
117 Johnston JL, Romsos DR, Bergen WG. Reduced brain norepinephrine metabolism in obese (ob/ob) mice is not normalized by tyrosine supplementation. J Nutr 1986;116(03):435–445
118 Li Z, Oben JA, Yang S, et al. Norepinephrine regulates hepatic innate immune system in leptin-deficient mice with nonalcoholic steatohepatitis. Hepatology 2004;40(02):434–441
119 Nishio T, Taura K, Iwaisako K, et al. Hepatic vagus nerve regulates Kupffer cell activation via α7 nicotinic acetylcholine receptor in nonalcoholic steatohepatitis. J Gastroenterol 2017;52(08): 965–976
120 Fonseca RC, Bassi GS, Brito CC, et al. Vagus nerve regulates the phagocytic and secretory activity of resident macrophages in the liver. Brain Behav Immun 2019;81:444–454
121 Roskams T, Yang SQ, Koteish A, et al. Oxidative stress and oval cell accumulation in mice and humans with alcoholic and nonalcoholic fatty liver disease. Am J Pathol 2003;163(04):1301–1311
122 Soeda J, Mouralidarane A, Ray S, et al. The β-adrenoceptor agonist isoproterenol rescues acetaminophen-injured livers through increasing progenitor numbers by Wnt in mice. Hepatology 2014;60(03):1023–1034
123 Yin C, Evason KJ, Asahina K, Stainier DY. Hepatic stellate cells in liver development, regeneration, and cancer. J Clin Invest 2013; 123(05):1902–1910

124 Kitto LJ, Henderson NC. Hepatic stellate cell regulation of liver regeneration and repair. Hepatol Commun 2020;5(03):358–370
125 Schachtrup C, Le Moan N, Passino MA, Akassoglou K. Hepatic stellate cells and astrocytes: stars of scar formation and tissue repair. Cell Cycle 2011;10(11):1764–1771
126 Cassiman D, van Pelt J, De Vos R, et al. Synaptophysin: a novel marker for human and rat hepatic stellate cells. Am J Pathol 1999;155(06):1831–1839
127 Buniatian G, Gebhardt R, Schrenk D, Hamprecht B. Colocalization of three types of intermediate filament proteins in perisinusoidal stellate cells: glial fibrillary acidic protein as a new cellular marker. Eur J Cell Biol 1996;70(01):23–32
128 Payen VL, Lavergne A, Alevra Sarika N, et al. Single-cell RNA sequencing of human liver reveals hepatic stellate cell heterogeneity. JHEP Rep 2021;3(03):100278
129 Rohn F, Kordes C, Buschmann T, et al. Impaired integrin α_5 /β_1 -mediated hepatocyte growth factor release by stellate cells of the aged liver. Aging Cell 2020;19(04):e13131
130 Oben JA, Diehl AM. Sympathetic nervous system regulation of liver repair. Anat Rec A Discov Mol Cell Evol Biol 2004;280(01): 874–883
131 Kordes C, Bock HH, Reichert D, May P, Häussinger D. Hepatic stellate cells: current state and open questions. Biol Chem 2021; 402(09):1021–1032
132 Oben JA, Yang S, Lin H, Ono M, Diehl AM. Norepinephrine and neuropeptide Y promote proliferation and collagen gene expression of hepatic myofibroblastic stellate cells. Biochem Biophys Res Commun 2003;302(04):685–690
133 Honda H, Ikejima K, Hirose M, et al. Leptin is required for fibrogenic responses induced by thioacetamide in the murine liver. Hepatology 2002;36(01):12–21
134 Dubuisson L, Desmoulière A, Decourt B, et al. Inhibition of rat liver fibrogenesis through noradrenergic antagonism. Hepatology 2002;35(02):325–331
135 Iwakiri Y. Pathophysiology of portal hypertension. Clin Liver Dis 2014;18(02):281–291
136 Ryou M, Stylopoulos N, Baffy G. Nonalcoholic fatty liver disease and portal hypertension. Explor Med 2020;1:149–169
137 Van der Graaff D, Kwanten WJ, Couturier FJ, et al. Severe steatosis induces portal hypertension by systemic arterial hyporeactivity and hepatic vasoconstrictor hyperreactivity in rats. Lab Invest 2018;98(10):1263–1275
138 Kurosawa M, Unno T, Aikawa Y, Yoneda M. Neural regulation of hepatic blood flow in rats: an in vivo study. Neurosci Lett 2002; 321(03):145–148
139 Hanson KM. Escape of the liver vasculature from adrenergic vasoconstriction. Proc Soc Exp Biol Med 1972;141(01):385–390
140 Greenway CV, Lawson AE, Mellander S. The effects of stimulation of the hepatic nerves, infusions of noradrenaline and occlusion of the carotid arteries on liver blood flow in the anaesthetized cat. J Physiol 1967;192(01):21–41
141 Lautt WW, Côté MG. Functional evaluation of 6-hydroxydopamine-induced sympathectomy in the liver of the cat. J Pharmacol Exp Ther 1976;198(03):562–567
142 Beckh K, Balks HJ, Jungermann K. Activation of glycogenolysis and norepinephrine overflow in the perfused rat liver during repetitive perivascular nerve stimulation. FEBS Lett 1982;149 (02):261–265
143 Henriksen JH, Ring-Larsen H, Kanstrup IL, Christensen NJ. Splanchnic and renal elimination and release of catecholamines in cirrhosis. Evidence of enhanced sympathetic nervous activity in patients with decompensated cirrhosis. Gut 1984;25(10): 1034–1043
144 Ueno T, Bioulac-Sage P, Balabaud C, Rosenbaum J. Innervation of the sinusoidal wall: regulation of the sinusoidal diameter. Anat Rec A Discov Mol Cell Evol Biol 2004;280(01):868–873
145 Ueno T, Tanikawa K. Intralobular innervation and lipocyte contractility in the liver. Nutrition 1997;13(02):141–148
146 Kostreva DR, Castaner A, Kampine JP. Reflex effects of hepatic baroreceptors on renal and cardiac sympathetic nerve activity. Am J Physiol 1980;238(05):R390–R394
147 Smith K. Liver disease: Kupffer cells regulate the progression of ALD and NAFLD. Nat Rev Gastroenterol Hepatol 2013;10(09):503
148 Chhatar S, Lal G. Role of adrenergic receptor signalling in neuroimmune communication. Curr Res Immunol 2021;2:202–217
149 Lamkin DM, Ho HY, Ong TH, et al. β-Adrenergic-stimulated macrophages: comprehensive localization in the M1-M2 spectrum. Brain Behav Immun 2016;57:338–346
150 Silva A, Caron A. Pathophysiological mechanisms that alter the autonomic brain-liver communication in metabolic diseases. Endocrinology 2021;162(11):162
151 Wang Z, Liang X, Lu Y, et al. Insomnia promotes hepatic steatosis in rats possibly by mediating sympathetic overactivation. Front Physiol 2021;12:734009
152 Kim D, Kim HJ, Kushida CA, Heo NY, Ahmed A, Kim WR. Short sleep duration is associated with abnormal serum aminotransferase activities and nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2018;16(04):588–590
153 Okamura T, Hashimoto Y, Hamaguchi M, Obora A, Kojima T, Fukui M. Short sleep duration is a risk of incident nonalcoholic fatty liver disease: a population-based longitudinal study. J Gastrointestin Liver Dis 2019;28(01):73–81
154 Prechtl JC, Powley TL. A light and electron microscopic examination of the vagal hepatic branch of the rat. Anat Embryol (Berl) 1987;176(01):115–126
155 Carnagarin R, Tan K, Adams L, et al. Metabolic dysfunction-associated fatty liver disease (MAFLD) - a condition associated with heightened sympathetic activation. Int J Mol Sci 2021;22 (08):22
156 Yi CX, la Fleur SE, Fliers E, Kalsbeek A. The role of the autonomic nervous liver innervation in the control of energy metabolism. Biochim Biophys Acta 2010;1802(04):416–431